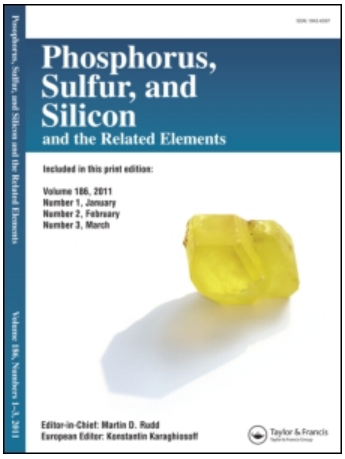

Phosphorus, Sulfur, and Silicon and the Related Elements

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ORGANIC DISULFIDES AND RELATED SUBSTANCES. 48. CYCLIC DI- AND TRISULFIDES BASED ON 1,4-DITHIOLS[1]

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ORGANIC DISULFIDES AND RELATED SUBSTANCES. 48. CYCLIC DI- AND TRISULFIDES BASED ON 1,4-DITHIOLS[1]

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Based on 1,4-dithiols, the seven-membered cyclic trisulfide 1,5-dihydro-2,3,4-benzotrithiepin (**3**), the nonbenzenoid counterpart (**17**), related oxides, and open-chain analogs were investigated. The monoxide **4a**, $n = 1$, of **3** upon oxidation lost sulfur and gave 1,4-dihydro-2,3-benzodithiin-2-monoxide (**12a**, $n = 1$). The 2,2-dioxide (**4b**, $n = 2$) could not be isolated; only **4a**, **12a**, or 1,4-dihydro-2,3-benzodithiin-2,2-dioxide (**12b**, $n = 2$) could be obtained. With related open-chain disulfides in the benzo series of the structure 1,2-$(RSSCH_2)_2C_6H_4$, when R was $-(CH_2)_4SO_2Na$, ca. 50% disproportionation occurred in H_2O in ca. 0.5 h, but the unsymmetrical disulfides with R = *p*-$CH_3C_6H_4$- or $HOCH_2CH(OH)CH_2$- were relatively stable. The nonbenzenoid counterpart of **3**, i.e. 4,7-dihydro-1,2,3-trithiepin (**17**) could not be obtained pure from the appropriate dichloride (**19a**), Bunte salt **16a** or thiosulfonate (**22a**), nor could be the *di*sulfide counterpart of **17**, i.e. 3,6-dihydro-1,2-dithiin (**23**), be oxidized to the 1,1-dioxide **24**. Bisdisulfides (**14ab**; **15ab**), however, could be obtained satisfactorily, as in the benzo series. Both *Z*-(**14a**) and *E*-disulfides (**15a**) could be obtained from the Bunte salt and thiosulfonate by reaction with *p*-toluenethiol; the *Z*-disulfide readily isomerized to the *E*-isomer. 2,3-Dihydroxypropanethiol also could be converted to the *Z* and *E* disulfides (**14b**, **15b**).

Key words: Disulfides; dithiins, 1,4-dithiols; sulfur (extrusion of); trisulfides; trithiepins.

INTRODUCTION

In continuing studies of di- and trisulfides,[2] we became interested in the cyclic trisulfide **3**, its nonbenzenoid counterpart **17**, and their oxides (Schemes I and II). Unexpected behavior with these cyclic di- and trisulfides led us to explore related reactions of open-chain disulfide counterparts (**1a–c**, **14a,b** and **15a,b**), since these had the common feature of also being derived from 1,4-dithiols. The trisulfide **3** had been prepared by the reaction of the Bunte salt **2** with Na_2S;[3] we were able to increase the yield to 73%, so that this method was better than our conversion of the dibromide **7** with Na_2S_3 (11%) or even of the thiosulfonate **11** with Na_2S (57%). The trisulfide **3** had been oxidized to the S-monoxide (**4a**, $n = 1$) with monoperphthalic acid in 40% yield (mp 133°C).[3]

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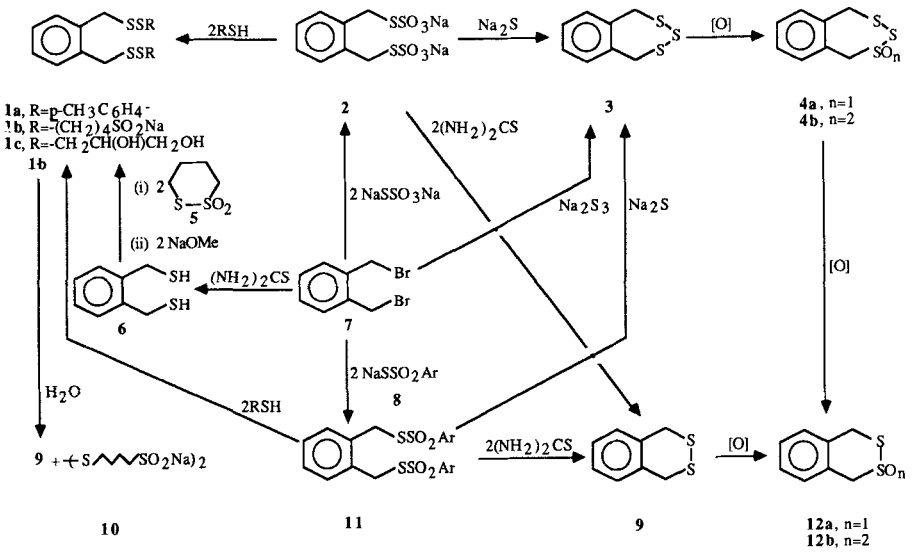
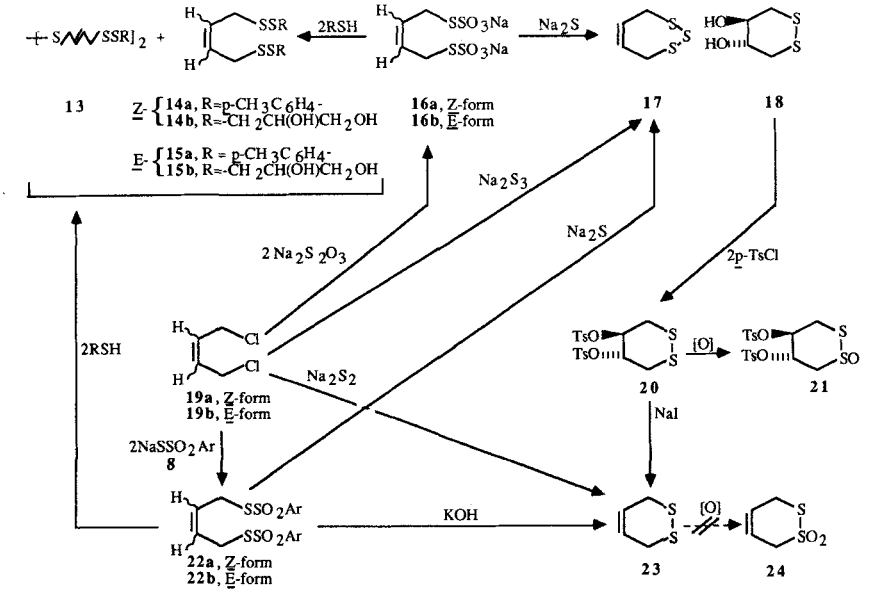


SCHEME I

RESULTS AND DISCUSSION

The unknown dioxide **4b** of **3** was a special objective for several reasons in our work, but it could not be isolated despite extensive efforts. For example, KIO_4 with **3** led to a TLC spot of R_f 0.38, which corresponded to loss of one sulfur atom from **4b** to give the *six*-membered dioxide **12b** (9% yield); a second spot (R_f 0.44), believed to be the seven-membered dioxide **4b**, was obtained immediately



SCHEME II

after oxidation in methanol but disappeared in a TLC done after ca. 2 h, during which the spot at R_f 0.38 increased at the expense of R_f 0.44. Furthermore, when the spot with R_f 0.44 was separated, a second TLC again showed both spots. Use of **3** with two or more molar proportions of *m*-chloroperoxybenzoic acid (MCPBA), H_2O_2, $NaBO_3 \cdot 4H_2O$ (useful for oxidizing sulfides to sulfoxides or sulfones),[4] or Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) led only to isolation of the monoxide **4a** ($n = 1$) in yields of 40–45%.

The identity of **12b** was proved by comparison with known **12b** obtained by another route, a novel reaction of a thiosulfonate (**11**) with thiourea, to give the known compound **9**,[3] followed by oxidation (Scheme I). In the oxidation of **9** to **12b**, incidentally, $NaBO_3$ gave the most consistent yield of pure product (ca. 42%), as usually proved true with similar compounds in this study; as an illustration of variability with KIO_4, although KIO_4 has given 60% yield in the oxidation of **9** to **12b**,[5] our present yield never exceeded ca. 40%, in a less clean reaction than with $NaBO_3$.

Oxidation of the seven-membered trisulfide **3** with four molar proportions of $NaBO_3$ gave the *six*-membered *mon*oxide (**12a**, $n = 1$) in 20% yield (perhaps via **4a**, which was isolated in 6% yield). The identity of **12a** was proved by synthesis from **9**.

In other experiments, use of large excesses of oxidants led to incorporation of more than two oxygen atoms into **3**, but the products were very sparingly soluble (probably partly polymeric) and could not be clearly separated chromatographically; titration with thiophenol by the method of Barnard and Cole for $—SO_2S—$ indicated incorporation of four oxygen atoms,[6] consistent with the moiety $—SO_2SSO_2—$.

In view of the unexpected loss of sulfur in oxidation of the trisulfide **3** and its monoxide **4a**, both of which contain the system $ArCH_2SS$, the analogous open-chain compounds **1a–c** containing $ArCH_2SS$ links were explored. The disulfide **1a** with $R = p\text{-}CH_3C_6H_4\text{-}$ could be obtained from the Bunte salt **2** but was best obtained from the thiosulfonate **11** (45–65%); it presented no extraordinary problems in stability. On the other hand, **1b** with $R = -(CH_2)_4SO_2Na$, obtained as shown in Scheme I from dithiol **6** and 1,2-dithiane 1,1-dioxide (**5**), disproportionates readily in water and 50% was lost in ca. 10 min; in methanol ca. 20% was lost in 0.5 h. After 8 h in water, **1b** disproportionated to the benzodithiin **9** in 90% yield; the other product of the disproportionation was **10**, as repeatedly observed in similar instances.[7] Unusually facile disproportionation of unsymmetrical disulfides containing the group $—(CH_2)_4SO_2Na$ has been noted before in a number of instances and has been attributed to a neighboring group attack of $—SO_2Na$ on the disulfide bond.[8] When R was $—CH_2CH(OH)CH_2OH$, **1c** was obtained by reaction of the appropriate thiol with the thiosulfonate **11**; since **1c** showed only a single spot in TLC, signifying no disproportionation, MS for both groups of this disulfide could be used to confirm the identity of **1c**. The approximate order of decreasing stability appeared to be **1a** > **1c** ≫ **1b**.

With respect to nonbenzenoid counterparts (Scheme II), Milligan and Swan prepared a Bunte salt (**16**) from the dichloride **19** (presumably both the salt and chloride were the *Z*-forms, **16a** and **19a**).[3] No attempts to convert the Bunte salt

to the cyclic trisulfide **17** were reported, nor were any other reactions of the Bunte salt.[3] Numerous efforts on our part to prepare **17** were unpromising. NMR and TLC indicated that reaction of the *Z*-halide **19a** with Na_2S_3 gave **17**, but the yield was quite low, and the **17** could not be purified. The *Z*-Bunte salt **16a** and thiosulfonate **22a** gave some improvement with Na_2S but insufficient to afford a feasible preparation. Others have had a similar experience with **16a**; **17** was isolated but only in less than 5% yield and still containing impurities, including **23**.[9]

In view of the outcome with **17**, further investigation of the known *six*-membered *di*sulfide counterpart of **17** (i.e. **23**) deserved attention. In contrast to the poor reaction mentioned of the *Z*-dichloride **19a** with Na_2S_3, reaction with Na_2S_2 afforded the best route to **23** (69%).[10] Although the *Z*-thiosulfonate **22a** could be prepared nicely from the *Z*-halide **19a** (75% yield),[1a] efforts to generate only one thiolate function with base (so that its attack on the remaining thiosulfonate function could generate **23**) led to **23** only in 8% yield (with two molar proportions of base, which proved better than one). Treatment of the ditosylate **20**, obtained from the diol **18**, with sodium iodide in acetone also produced **23** but in low yield (sodium iodide has been used to demesylate *vic*-dimesylates to give alkenes).[11]

As with the *seven*-membered trisulfide **3**, the *six*-membered disulfide **23** also could not be converted to 3,6-dihydro-1,2-dithiin 1,1-dioxide (**24**). Agents tried were KIO_4, $NaIO_4$, $NaBO_3$, Oxone®, H_2O_2, MCPBA, and $Ph_3P{\cdot}O_3$; cleavage of allylic-sulfur bonds seem to have been at least a partial cause, since sulfate ion was formed with several of the oxidants. Similarly, although **20** could be oxidized to the monoxide **21** (69% yield), sodium iodide in acetone did not convert **21** to the monoxide counterpart of the dioxide **24**, although sodium *p*-toluenesulfonate could be isolated in 100% yield. *cis*-1,2-Dithiane-4,5-diol could not be converted to the ditosylate for similar studies with sodium iodide.

As with the benzo series (Scheme I), nonbenzenoid disulfides could be obtained satisfactorily. The *Z*-(**16a**) and *E*-(**16b**) Bunte salts both could be converted to the bis-*p*-tolyl disulfides **14a** and **15a** in yields of 34–67%. The *Z*-(**22a**) and *E*-(**22b**) thiosulfonates also could be used. The thiosulfonates were obtained from the appropriate dichlorides (Scheme II);[1] the *Z*-form **14a** isomerized to the *E* form (**15a**) to a considerable extent under ambient conditions overnight. The route from the thiosulfonates is quicker than from the Bunte salts. The *Z*- and *E*-thiosulfonates also could be converted to **14b** and **15b** where R was $-CH_2CH(OH)CH_2OH$; the Z form isomerized fairly readily to the E form, although probably less readily than in the tolyl series. Since TLC showed only a single spot, signifying no disproportionation, MS for both groups of the disulfides confirmed identity, as with **1c**.

In all preparations of the unsymmetrical disulfides, the dimer-type product **13** was obtained in 6–11% yield (**13** can be envisioned as arising from a disproportionation involving only one of the two disulfide links of **14a,b** or **15a,b**). A cautionary note is warranted *vis-à-vis* the preparation of the *p*-tolyl *Z*-disulfide (**14a**): conditions other than those carefully worked out (see Experimental Section), or exposure to warmth or light, led to significant conversion to the *E*-isomer. The *Z*-isomer of the hydroxyalkyl compound **14b** was less sensitive.

Our conclusions as to the di- and trisulfides studied, based on 1,4-dithiols, can be summarized as follows: (1) Although the seven-membered trithiepin **3** is known to be oxidizable to the S-monoxide, the S,S-dioxide could not be isolated; only the S-monoxide or a six-membered monoxide or dioxide were obtainable. (2) The nonbenzenoid trithiepin **17** could not be satisfactorily synthesized, and efforts failed to obtain even the six-membered dioxide. (3) On the other hand, disulfide derivatives of 1,4-dithiols having the $ArCH_2SSR$ moiety in an open-chain rather than a cyclic environment were reasonably stable when R was a typical aryl or hydroxyalkyl group (although not when R was a sulfinoalkyl group).

EXPERIMENTAL

Melting points were determined on a Thomas Hoover stirred-liquid apparatus and are corrected. ^{1}H NMR spectra were recorded on a JEOL-FX-90Q (90 MHz) or IBM NR/300 FT NMR (300 MHz) spectrometer and ^{13}C NMR spectra on a JEOL-FX-90Q spectrometer operating at 22.5 MHz in deuterated solvents (e.g. D_2O with $Me_3Si(CH_2)_3SO_3Na$ or Me_4Si with MeOH-d_4, Me_2CO-d_6 or $CDCl_3$). Chemical shifts are reported in ppm (δ). A doublet resonance, with an additional small line very close (ca. 1 Hz away) towards the inner side of either of the peaks (arising from long range coupling), has been regarded as a doublet only. IR spectra were recorded on a Perkin-Elmer Model 727 spectrometer using neat liquids or Nujol mulls; usually, only strong bands are specified (s). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Mass spectra were obtained on a VG 70-250 GC-MS instrument equipped for electron impact (EI) and fast atom bombardment (FAB) mass spectrometry. EI-MS was carried out in exact mass mode with the instrument set to a resolving power of 10,000. Reported data were obtained by spectral averaging (funding provided by the NIH, Division of Research Resources Grant RR01688). Analytical TLC was performed on silica gel (Eastman Chromagram, catalog no. 13181) with visualization by UV or I_2 vapor. Preparative TLC was done on Whatman PLK5F (1000 μ) or LK5F (250 μ) plates. Moist solutions were dried over anhydrous $MgSO_4$ and then solvents were removed on a Büchi Rotavapor-R under reduced pressure and then on an oil pump. Baker 7024 silica gel (40-μm average particle diameter) was used for flash chromatography, and the crude sample (to be separated) was loaded after adsorbing it on a small amount of silica gel. All solvents were degassed by bubbling Ar through them for 15 min.

The following were prepared essentially as reported: *Disodium 1,2-di(sulfothiomethyl)benzene*,[3] **2**·1.5H_2O [yield 78%, lit.[3] 37%; ^{1}H NMR (D_2O)δ 7.57–7.25 (m, 4H), 4.45 (s, 4H); ^{13}C NMR (D_2O) δ 137.44, 133.54, 131.05, 38.84; IR (Nujol) 3500 (br), 1635, 1240–1180s, 1155, 1055s, 1030s, 845, 775, 710s cm^{-1}]; *α,α'-dimercapto-o-xylene*,[5] **6** [yield 47%, lit.[5] 82%; mp 44.5–46°C, lit.[12a] 46–48°C; ^{1}H NMR (consistent with report)[12b] ($CDCl_3$) δ 7.30–7.21 (m, 4H), 3.86 (d, J = 7.1 Hz, 4H), 1.85 (t, J = 7.1 Hz, 2H); IR (Nujol) 2575, 1600w, 1500w, 1420, 1245, 1190, 1080, 965, 850, 760s, 740, 720, 665s cm^{-1}]; *disodium 4,4'-dithiobis(butanesulfinate)* **10**;[7a] *1,2-bis(p-tolylsulfonylthiomethyl)benzene* (**11**);[1a] Na_2S_2 (Na_2S_3 was prepared similarly but with more sulfur);[10] *disodium Z-2-butene-1,4-bisthiosulfate*, **16a**·*1.0*H_2O [yield 85%, lit.[3] 58%]; **E-19b** was black technical *trans-1,4-dichloro-2-butene* purified by passage through a short column of silica-gel; *Z*- and *E-1,4-bis(p-tolylsulfonylthio)-2-butenes* (**22a** and **22b**, respectively).[1a] "Buffer solution" refers to 0.05 M phosphate buffer, pH 7. Other materials were commercial unless otherwise specified.

1,5-Dihydro-2,3,4-benzotrithiepin (**3**). (*a*) *From the Bunte salt* **2**. The procedure of Milligan and Swan was used with 9.61 g (40.0 mmol) of $Na_2S·9H_2O$ in H_2O (80 mL) which was added to the Bunte salt **2**·1.5H_2O (16.06 g, 40.0 mmol), and H_2CO (2.40 g, 80.0 mmol i.e. ca. 8 mL of 30% solution) in pH 7 buffer solution (400 mL), pH 7, rather than 0.25 M, pH 8.[3] The pH was maintained by simultaneous dropwise addition (1 h) of HCl (ca. 12.5 mL of 1.5 N). White solid that precipitated was separated by filtration and dried simply by pressing well on a filter during 1 h (perhaps 1–2 mL of H_2O remained; complete drying in vacuo led to polymerization). The partly dried product then was carefully heated with boiling hexane (3 × 100 mL), which on cooling gave 5.88 g (73%, lit.[3] 48%) of shining flaky crystals of **3**: mp 100–101.5°C (lit.[3] 101–102°C); ^{1}H NMR (consistent with refs. 9, 12a) ($CDCl_3$) δ 7.16 (s, 4H), 4.87–4.18 (dd, with a small singlet at 4.13, 4H); IR (Nujol) 1660, 1420s, 1300, 1240, 1180, 1080, 950, 885, 850, 830, 770s, 720, 665s cm^{-1}.

(*b*) *From α,α'-dibromo-o-xylene* (**7**). A solution of Na_2S_3 (3.09 g, 21.8 mmol) [freshly prepared by adding 2.09 g (65.3 mg atom) of sulfur to 1.00 g (43.5 mg atom) of Na in 200 mL of liquid NH_3 at −70 to −80°C under Ar] in MeOH (75 mL) was added dropwise to a stirred solution of **7** (5.74 g, 21.7 mmol) in MeOH (75 mL) at 25°C over 30 min. After a stirring period of 1 h, crude solid **3** separated which on purification from boiling hexane gave the pure trisulfide **3**; 0.48 g (11%): mp 100–101.5°C; IR and NMR spectra were identical with those obtained in (a). MS (EI) exact mass found 199.9786 (30), $C_8H_8S_3$ requires 199.9788; m/z 168 (30) (M-S), 135 (100) ($M-S_2$), 104 (35) ($M-S_3$), 91 (8) (C_7H_7).

Anal. Calcd for $C_8H_8S_3$: C, 47.97; H, 4.02; S, 48.01. Found: C, 47.95; H, 4.09; S, 47.78.

(*c*) *From thiosulfonate* **11**. A solution of $Na_2S{\cdot}9H_2O$ (0.25 g, 1.05 mmol) in H_2O (15 mL) was added (30 min) to the solution-cum-suspension of thiosulfonate **11** (0.50 g, 1.05 mmol) in MeOH (50 mL) at 25°C. After an additional 2 h of stirring (TLC), the mixture was extracted with hexane (3 × 25 mL). The hexane was washed with H_2O, dried, and concentrated to give **3** as white crystalline solid; yield 0.12 g (57%): mp 100–101.5°C; IR and NMR as in (a).

1,4-Dihydro-2,3-benzodithiin (**9**).

(*a*) *From the Bunte salt* **2**. By means of a reported procedure,[3] the Bunte salt **2**·1.5H_2O gave 65% of **9**: mp 77–77.5°C (lit.[3] 77–78°C); ^1H NMR (consistent with report)[3] ($CDCl_3$) δ 7.15–7.05 (m, 4H), 4.05 (s, 4H).

(*b*) *From the thiosulfonate* **11**. Thiosulfonate **11** (0.50 g, 1.05 mmol), thiourea (0.16 g, 2.10 mmol), and 10 mL of 1N HCl were heated for 30 min at 80°C and then cooled. Solvent was removed and the residue was extracted with CH_2Cl_2 (2 × 20 mL). Drying and concentration gave **9** as crude solid, which after two recrystallizations from hexane furnished 0.008 g (5%) of **9**; the mp, IR, and NMR spectra were identical with those of authentic **9**.

Oxidation of **3** *with Isolation of the Dioxide* **12b** *via Use of* KIO_4. A solution of trisulfide **3** (2.00 g, 9.98 mmol) in *i*-PrOH (400 mL) was added (1 h) to a stirred suspension of KIO_4 (6.89 g, 30.0 mmol) in H_2O (200 mL) at 80°C containing a crystal of I_2. After 2 h, solvent was removed at ca. 40°C, residue was extracted with $CHCl_3$ (3 × 50 mL), and the extract was dried and concentrated to give a crude purple solid, which was washed gently with cold benzene. The 0.65 g of white solid showed two spots: R_f 0.38, and 0.44 (20% EtOAc in hexane). Chromatographic separation on a silica gel column (30-mm diameter) using 10% EtOAc in hexane afforded only one component (R_f 0.38); yield, 0.170 g of **12b** (9%). Several attempts to isolate the upper spot (R_f 0.44) even by preparative TLC failed, because of the instability of the trisulfide dioxide **4b**; the spot at 0.44 disappeared and that at 0.38 increased. The instability of **4b** also was supported by the formation of **12b**. The **12b** had mp 106–107°C (lit.[5] 108–109°C); ^1H NMR ($CDCl_3$) δ 7.33–7.13 (m, 4H), 4.61 (s, 2H), 4.55 (s, 2H); IR (consistent with report)[5] (Nujol) 1600, 1295s, 1260, 1240, 1180, 1150, 1140, 1125s, 1110s, 1090, 770, 720 cm^{-1}.

Anal. Calcd for $C_8H_8O_2S_2$: C, 47.98; H, 4.03; S, 32.02. Found: C, 47.45; H, 4.05; S, 32.32.

Oxidation of the disulfide **9** to **12b** was explored with several oxidizing agents: (*a*) KIO_4.[5] A standard method for reaction of **9** with KIO_4 in *i*-PrOH-H_2O (2:1) at 80°C for 4 h furnished **12b** in 35–40% yield (lit.[5] 60%): mp 106–107°C (lit.[5] 108–109°C); IR and NMR spectra identical with those of **12b** from **3**. (*b*) $NaBO_3{\cdot}4H_2O$. A solution of $NaBO_3{\cdot}4H_2O$ (0.274 g, 1.78 mmol) in AcOH was added to the stirred solution of **9** (0.100 g, 0.59 mmol) in AcOH (7 mL) at 25°C over 10 min and the mixture then stirred for 24 h. Solvent removal and extraction with EtOAc gave solid, which on crystallization from MeOH gave 0.05 g (42%) of **12b**: mp 106–107°C. (*c*) *Oxone®*. Oxidation of **9** (0.100 g, 0.59 mmol) with Oxone® (0.73 g, 1.19 mmol; $2KHSO_5 \equiv 1$ Oxone®) in 1:1 MeOH-H_2O mixture (6 mL) after 24 h afforded 0.022 g (19%) of **12b** (mp 106–107°C) after solvent removal, extraction (EtOAc) and purification.

1,5-Dihydro-2,3-4-benzotrithiepin-2-oxide (**4a**).

(*a*) *Via* $NaBO_3$. A solution of $NaBO_3{\cdot}4H_2O$ (1.92 g, 12.5 mmol) in AcOH (20 mL) was added (30 min) to a stirred solution of benzotrithiepin **3** (1.00 g, 4.99 mmol) in AcOH (40 mL) at 25°C. After 2 h of stirring, solvent was removed to dryness, the residue was dissolved in hot EtOAc (50 mL), and the filtrate was concentrated to give the crude product. Another dissolution of the above crude in EtOAc, filtration through Celite, concentration, and cooling at 0°C gave **4a** as yellow crystalline solid, 0.54 g (50%), mp 118–132°C. Purification and recrystallization from $CHCl_3$ using decolorizing carbon afforded slightly yellowish crystals of pure **4a**, 0.48 g, 44% (lit.[3] 40%): mp 135–137°C (lit.[3] 133°C); R_f

0.25 (20% EtOAc-hexane); IR and NMR spectra consistent with reported values[3] [IR (Nujol) 1410, 1180, 1090s, 1070s, 950, 900, 865, 780s, 760s, 720 cm^{-1}; NMR ($CDCl_3$) δ 7.45–7.13 (m, 4H), 4.57–4.17 (dd, 2H), 4.45–4.07 (dd, 2H)] MS(FAB+, tetramethylene sulfone) 217 (MH); (FAB−) 216(M), 200 (M-O), 184 (M-S), 183 (M-SH).

Anal. Calcd for $C_8H_8OS_3$: C, 44.42; H, 3.73; S, 44.46. Found: C, 44.73; H, 3.93; S, 44.46.

Use of two molar proportions of $NaBO_3 \cdot 4H_2O$ with the monoxide **4a** gave only **12a** in ca. 20% yield, with no indication of **4b**.

(*b*) *Via m-chloroperoxybenzoic acid* (*MCPBA*). A solution of MCPBA (1.29 g, 7.49 mmol) in Et_2O (50 mL) was added slowly (2.5 h) to a stirred solution of **3** (1.00 g, 4.99 mmol) in Et_2O (50 mL) at 25°C. After overnight stirring the precipitated **4a** was removed. Further purification as usual gave 0.49 g (45%) of pure **4a**: mp 135–137°C; IR and NMR spectra identical with **4a** obtained in (a).

(*c*) *Via* H_2O_2. A solution of H_2O_2 (9.71 mmol, i.e. ca. 1.1 mL of 30% aq. solution) in AcOH (15 mL) was added dropwise (1 h) to the stirred solution of the **3** (1.00 g, 4.99 mmol) in AcOH (50 mL) at 25°C with additional stirring for 7 h. Solvent removal and workup gave crude **4a** which was chromatographed on a silica gel column (40-mm diameter) using 10–15% EtOAc-hexane to yield 0.43 g (40%) of **4a**; mp 135–137°C; IR, and NMR spectra identical with **4a** in (a).

1,4-Dihydro-2,3-benzodithiin-2-oxide (**12a**). A solution of $NaBO_3 \cdot 4H_2O$ (0.914 g, 5.94 mmol) in AcOH (20 mL) was added (10 min) to the stirred solution of **9** (0.50 g, 2.97 mmol) in AcOH (25 mL) at 25°C. After a total period of 1 h, solvent was removed, and residue was extracted with hot $CHCl_3$ (50 mL). The extract was filtered through Celite and then through a small silica gel column. Concentration of the clear filtrate gave 0.47 g (86%) of crude solid. Further purification was achieved by a quick low temperature crystallization from MeOH to yield 0.40 g (73%) of pure **12a** as fine white needles: mp 128–129°C; R_f 0.18 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$) δ 7.42–7.24 (m, 4H), 4.38–3.92 (8 lines, 4H); ^{13}C NMR ($CDCl_3$) δ 135.67, 131.66, 129.17, 128.30, 128.03, 127.60, 59.88, 32.79; IR (Nujol) 1305, 1180, 1120, 1075s, 760, 720 cm^{-1}; MS(FAB+, tetraethylene glycol) 185 (MH); (FAB−) 184 (M), 183 (M-H).

Anal. Calcd for $C_8H_8OS_2$: C, 52.14; H, 4.38; S, 34.80. Found: C, 52.02, H, 4.49; S, 34.64.

Oxidation of Trithiepin **3** *to* **4a** *and* **12a**. A solution of $NaBO_3$ (3.07 g, 19.95 mmol) in AcOH (30 mL) was added (1 h) to a stirred solution of **3** (1.00 g, 4.99 mmol) in AcOH (40 mL) at 25°C. Additional stirring was continued for 24 h at 25°C and then for 48 h at 48–50°C (TLC showed two spots, R_f 0.25 and 0.18; 20% EtOAc in hexane). Removal of solvent, followed by extraction ($CHCl_3$), afforded a crude material which was chromatographed on a silica gel column (41-mm diameter) using 10–15% EtOAc in hexane to give 0.060 g (6%) of **4a** (R_f 0.25) and 0.180 g (20%) of **12a** (R_f 0.18). The **4a** and **12a** had mp, IR, and NMR spectra identical with authentic samples.

1,2-Bis(p-tolyldithiomethyl)benzene (**1a, R = p-$CH_3C_6H_4$−**).

(*a*) *From the reaction of p-toluenethiol with the thiosulfonate* **11**. A solution of *p*-toluenethiol (0.130 g, 1.05 mmol) in MeOH (5 mL) was added slowly (30 min) to the stirred solution of **11** (0.250 g, 0.52 mmol) in CH_2Cl_2 (20 mL) at 5°C under Ar in the dark; the reaction then was complete (TLC). The mixture was concentrated and then extracted with CH_2Cl_2 (2 × 25 mL). The extract was washed with H_2O, dried and concentrated to give an oil. Chromatographic separation on a silica gel column (17-mm diameter) using hexane-5% CH_2Cl_2 in hexane yielded 0.140 g (65%) of **1a** as slightly yellowish viscous liquid: R_f 0.45 (10% CH_2Cl_2 in hexane); ^1H NMR ($CDCl_3$) δ 7.31–7.08 (dd, 8H), 7.17 (s, 4H), 4.01 (s, 4H), 2.33 (s, 6H); IR (neat) 3090–2870, 1705, 1625, 1600, 1485s, 1300, 1100, 1010, 900, 800s, 760, 730s cm^{-1}.

Anal. Calcd for $C_{22}H_{22}S_4$: C, 63.72; H, 5.35; S, 30.93. Found: C, 63.15; H, 5.42; S, 30.56.

Neat **1a** remained unchanged after 24 h in ambient conditions, whereas a methanolic solution of **1a** began to disproportionate after ca. 10–12 h (TLC).

(*b*) *From the reaction of p-toluenethiol with the Bunte salt* **2**. A solution of sodium *p*-toluenethiolate freshly prepared from *p*-toluenethiol (2.48 g, 20.0 mmol) and sodium (0.46 g, 20.0 mg atom) in MeOH (15 mL), was added slowly (45 min) to the stirred solution of **2**·1.5H_2O (4.01 g, 10.0 mmol) in pH 7 buffer solution (70 mL) at 5–10°C. A neutral pH was maintained by addition of 1.5 N HCl. The mixture was extracted (CH_2Cl_2), and the crude oil was chromatographed as in (a) to give 1.10 g (27%) of **1a**. TLC, IR and NMR spectra were identical with those of **1a** obtained in (a).

Disodium 1,2-Bis(4'-sulfinobutyldithiomethyl)benzene (**1b, R = $(CH_2)_4SO_2Na$**). The dithiane dioxide **5** (0.761 g, 5.00 mmol), and dithiol **6** (0.425 g, 2.50 mmol) were stirred in 1:1 $CHCl_3$—MeOH

(10 mL) at 5°C for 5 min under Ar. A solution of NaOMe prepared from Na (0.115 g, 5.00 mg atom) in MeOH (5 mL), then was added (0.5 min). After 10 min more the clear solution was quickly diluted with Et_2O (200 mL); the resulting precipitate was centrifuged and dried to yield 1.14 g (87%) of **1b**·0.3H_2O as white hygroscopic solid: R_f 0.54 (40% MeOH in Me_2CO); ^{1}H NMR (MeOH-d_4) δ 7.35–7.22 (m, 4H), 4.14 (s, 4H), 2.39 (t, 4H), 2.20 (t, 4H), 1.68–1.54 (m, 8H); IR (Nujol) 3450 (br), 1670, 1490, 1410, 1310, 1280, 1230, 1020–980s (br), 770, 730, 705 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}Na_2O_4S_6$·0.3H_2O: C, 36.67; H, 4.73; S, 36.70. Found: C, 36.86; H, 4.78; S, 36.83. %H_2O loss calcd for **1b**·0.3H_2O→**1b** (anhyd): 1.03. Found: 1.04.

Disproportionation of **1b** *in* H_2O *to Give* **9** *and* **10**. An aqueous solution of **1b** became milky in less than one min after dissolution, indicating a high degree of instability of **1b** in H_2O. A quantitative estimation was made by dissolving a 0.500 g sample of **1b** in 10 mL of H_2O at 25°C followed by periodical extractions of **9**, as one of the disproportionation products, by Et_2O; 43% disproportionation occurred in <1 min and 90% after ca. 5 h. The time for survival of 50% of **1b** was ca. 10 min.

Stability of **1b** in MeOH-d_4 was estimated by NMR, based on the relative integrals for **1b** and the bissulfinate **10**. After 0.5 h, ca. 80% of **1a** survived, whereas only 23% was left in MeOH-d_4 under ambient conditions after 24 h.

1,2Bis(2′,3′-dihydroxypropyldithiomethyl)benzene [**1c**, **R** = −$CH_2CH(OH)CH_2OH$]. A solution of 2,3-dihydroxypropanethiol (0.117 g, 1.08 mmol) in CH_2Cl_2 (4 mL) was added (10 min) to a stirred solution of **11** (0.258 g, 0.54 mmol) in CH_2Cl_2 (8 mL) at 0°C under Ar in the dark, and the mixture was stirred until TLC showed no further change at 15°C (1 h). Solvent was removed and the crude **1c** was separated on a silica gel column (17-mm diameter) using 5–7% MeOH in CH_2Cl_2 to yield 0.025 g (12%) of **1c** as highly viscous oil: R_f 0.38 (10% MeOH in CH_2Cl_2); ^{1}H NMR (MeOH-d_4) δ 7.34–7.23 (m, 4H), 4.15 (s, 4H), 3.79–3.75 (m, 2H), 3.53–3.42 (m, 4H), 2.66–2.50 (4d, 8 lines, 4H); IR (neat) 3400s (br), 2940s, 1600, 1490, 1455, 1410, 1330, 1285, 1230, 1070s, 1030s, 880, 810, 765, 690 cm^{-1}. MS (EI): sample evolved from the direct introduction probe at ca. 100°C; (exact mass found, formula, mmu error); 246.0065, $C_6H_{14}S_3O_4$, −1.1; 214.0332, $C_6H_{14}S_2O_4$, −0.2; 168.0053, $C_8H_8S_2$, 1.5; 135.0262, C_8H_7S, 0.6; 104.0621, C_8H_8, 0.5, all consistent with plausible fragment ions from structure **1c**. TLC indicated that disproportionation of **1c** in MeOH began in ca. 8–9 h under ambient conditions.

trans-1,2-Dithiane-4,5-diol Ditosylate (**20**). Based on a reported method,[13] *p*-toluenesulfonyl chloride (17.55 g, 92.1 mmol) was added in portions to a well stirred solution of the *trans*-diol **18** (3.50 g, 23.0 mmol) in pyridine (125 mL) at 0°C over a period of 1 h. The mixture was stirred for 2 h more at 0°C, for 25 h at ca. 25°C and then for 32 h at ca. 35°C, whereupon reaction was complete (TLC). Pyridine was removed, and oily residue was extracted with $CHCl_3$ (3 × 150 mL). The organic extract was washed with dilute aqueous HCl, brine, H_2O, and then dried and concentrated to give 11.00 g of thick reddish-brown oil, which partly solidified under vacuum (12 h, 0.1 torr). Rubbing with cold Et_2O left 4.45 g (42%) of **20** as white crystalline solid: mp 105–106°C; R_f 0.38 (20% EtOAc in hexane); ^{1}H NMR (Me_2CO-d_6) δ 7.67–7.30 (dd, 8H), 4.53–4.50 (m, 2H), 3.34–3.30 (dd, 2H), 3.17–2.97 (br, m, 2H) 2.43 (s, 6H); ^{13}C NMR (Me_2CO-d_6) δ 146.38, 134.63, 130.94, 128.91, 77.99, 39.58, 21.68; IR (Nujol) 1600, 1410, 1360s, 1310, 1295, 1190, 1175s, 1095, 1015, 950s, 890, 835s, 810, 740, 670s cm^{-1}.

Anal. Calcd for $C_{18}H_{20}O_6S_4$: C, 46.94; H, 4.38; S, 27.84. Found: C, 47.09; H, 4.55; S, 27.89.

3,6-Dihydro-1,2-dithiin (**23**).

(*a*) *From the Dichloride* **19a**. By means of a reported procedure,[10] from freshly prepared Na_2S_2 (11.01 g, 100.0 mmol)[10] and *Z*-1,4-dichloro-2-butene (12.50 g, 100.0 mmol), 8.14 g (69%; reported 55–60%)[10] of **23** was obtained as colorless mobile liquid after flash chromatography using a silica gel column (50-mm diameter × 15 cm) with pentane: R_f 0.5 (100% pentane); ^{1}H NMR (consistent with report)[10] ($CDCl_3$) δ 5.98 (t, 2H), 3.27 (d, 4H); IR (neat) 3025, 2900s, 1650, 1395s, 1380, 1245, 1210, 1150, 995, 895, 805s, 775, 625s cm^{-1}.

(*b*) *From the thiosulfonate* **22a**. A solution of *Z*-thiosulfonate **22a** (0.700 g, 1.63 mmol) in MeOH (20 mL, made by heating and then cooling to 35°C) was added to stirred methanolic-KOH (3.26 mmol, i.e. ca. 10 mL of 1.83% solution) at 15°C over 0.5 h followed by further stirring at 25°C for 1 h. Solvent was reduced to ca. 5 mL and a pentane extract (3 × 15 mL) was washed with H_2O, dried, and passed through a small silica gel column (10-mm diameter; 5 g of silica gel) to give 0.015 g (8%) of **23**. R_f, IR and NMR spectra were identical with those of **23** obtained from **19a** in (a).

(*c*) *From the bistosylate* **20**. A solution of NaI (0.391 g, 2.61 mmol) in Me_2CO (8 mL) was added (15 min) to the stirred solution of **20** (0.400 g, 0.87 mmol) in Me_2CO (8 mL) at ca. 25°C under Ar in the dark. After 20 h of reflux with an efficient condenser, solid that separated was removed by filtration and discarded. The filtrate was evaporated, and a hexane extract was purified as above to give 0.010 g (10%) of **23** having spectra essentially as described above.

trans-1,2-Dithiane-4,5-diol Ditosylate 1-Oxide (**21**). A solution of $NaBO_3 \cdot 4H_2O$ (3.00 g, 19.50 mmol) in AcOH (30 mL) was added to a stirred solution of **20** (3.00 g, 6.51 mmol) in AcOH (120 mL) at 25°C during 15 min. After a total period of 35 min, when TLC showed a single spot, solvent was removed, the residue was extracted with hot Me_2CO (100 mL), insoluble borate was discarded, and the filtrate was passed through Celite. The clear solution thus obtained was concentrated to give crude **21** as a solid in ca. 93% yield; mp 118–125°C. The crude **21** was dissolved in hot MeOH (100 mL), which was cooled quickly to 25°C, when product began to crystallize, and then at 0°C overnight to yield 2.15 g (69%) of **21**: mp 131–133°C; R_f 0.22 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) δ 7.71–7.23 (m, 8H), 5.20–5.09 (t, mixed, 1H), 4.82–4.71 (t, mixed, 1H), 3.88–3.71 (m, 2H), 3.38–3.13 (m, 2H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (Me_2CO-d_6) δ 146.5, 130.94, 129.00, 78.34, 73.36, 60.08, 21.67; IR (Nujol) 1595, 1500, 1370s, 1345, 1310, 1255, 1215, 1190, 1175s, 1145, 1095, 1070, 1015, 970bs, 880, 835, 820, 750, 705, 685, 665 cm^{-1}; MS (FAB+, 5:1 dithiothreitol:dithioerythritol) 477 (MH+), 305 (MH − $C_7H_7SO_3$), 289 (MH − $C_7H_7SO_3$ − O); (EI, 15 eV) 460 (25) (M − O), 304 (25) (M − $C_7H_7SO_3H$), 172 (100) ($C_7H_7SO_3H$) and 155 (70) ($C_7H_7SO_2$).

Anal. Calcd for $C_{18}H_{20}O_7S_4$: C, 45.36; H, 4.23; S, 26.91. Found: C, 44.91; H, 4.33; S, 26.95.

Disodium E-2-Butene-1,4-bisthiosulfate (**16b**). The same procedure as for **16a** was used,[3] except that crystallization was done from a 2:1 EtOH-MeOH mixture. Starting from 12.50 g (100.0 mmol) of *E*-1,4-dichloro-2-butene (**19b**) and 31.62 g (200.0 mmol) of anhydrous $Na_2S_2O_3$, after reflux in 400 mL of 50% EtOH-H_2O for 3 h, 20.00 g (61%) of **16b**·0.1H_2O was obtained (the analytical sample was prepared by washing **16b** with Me_2CO and CH_2Cl_2, and then recrystallizing from MeOH and drying under vacuum (0.1 torr for 24 h): ^{1}H NMR (D_2O) δ 5.77–5.74 (m, 2H), 3.60 (d, J = 5.8 Hz, 4H); IR (Nujol) 3550 (br), 1640, 1240–1185s (br), 1040s, 960, 890, 725, 640s cm^{-1}.

Anal. Calcd for $C_4H_6Na_2O_6S_4 \cdot 0.1H_2O$: C, 14.73; H, 1.92; S, 39.32. Found: C, 14.71; H, 1.93; S, 39.30. H_2O calcd for **16b**·0.1H_2O → **16b** (anhyd): 0.55. Found: 0.70.

Z-1,4-Bis(p-tolyldithio)-2-butene (**14a, R = p-$CH_3C_6H_4$**).

(*a*) *From the Z-Bunte salt* **16a**. A solution of *p*-toluenethiol (0.621 g, 5.00 mmol) in aqueous NaOH (0.200 g, 5.00 mmol in 15 mL of H_2O) was added (5 min) to the stirred solution of the *Z*-Bunte salt **16a**·1H_2O (0.952 g, 2.78 mmol) in pH 7 buffer solution (50 mL) in the dark at −5°C. After 10 min of stirring, the mixture was quickly worked up by extracting with $CHCl_3$ (3 × 50 mL). The extract was washed with cold water (10–15°C), dried, and concentrated to give viscous oil which on a silica gel column (40-mm diameter × 15 cm) using 100% hexane to 5% CH_2Cl_2 in hexane, afforded 0.310 g (34%) of **14a** as highly viscous oil: R_f 0.52 (10% CH_2Cl_2 in hexane); ^{1}H NMR ($CDCl_3$) δ 7.37–7.09 (dd, 8H), 5.64 (t, J = 5.2 Hz, 2H), 3.36 (d, J = 6.9 Hz, 4H), 2.32 (s, 6H); IR (neat) 3040–2875, 1600, 1490s, 1400, 1305, 1210, 1180, 1120, 1080, 1020, 805s cm^{-1}; MS (EI): exact mass found 364.0049 (4), $C_{18}H_{20}S_4$ requires 364.0048; m/z (rel. intensity, %) 278 (17), 247 (4), 211 (9), 210 (14), 209 (100), 187 (16), 157 (15), 156 (18), 124 (25), 123 (55), 122 (7), 121 (9), 109 (3), 108 (3).

Anal. Calcd for $C_{18}H_{20}S_4$: C, 59.30; H, 5.53; S, 35.17. Found: C, 59.20; H, 5.61; S, 35.00.

A small amount (0.038 g, 6% yield, based on *p*-toluenethiol) of 1-(*p*-tolyldithio-*E*-2-butenyl) disulfide (**13**) also was isolated as the second fraction from the chromatogram as a viscous oil: R_f 0.31 (10% CH_2Cl_2 in hexane); ^{1}H NMR ($CDCl_3$) δ 7.39–7.11 (dd, 8H), 5.68–5.54 (m, 4H), 3.45–3.20 (m, 8H), 2.31 (s, 6H); IR (neat) 3050–2875, 1600, 1490s, 1410, 1305, 1210, 1180, 1115, 1080, 1015, 965s, 805s, 730s cm^{-1}; MS: m/z (rel. intensity, %) 482 (2, M^+), 396 (1.9), 364 (2.5), 359 (3), 327 (9), 310 (2), 295 (3), 279 (2), 278 (11), 273 (5), 246 (2), 241 (2), 2.14 (2), 210 (14), 209 (100), 208 (2), 188 (2), 187 (17), 178 (2), 177 (18), 176 (2), 175 (1), 163 (2), 156 (10), 154 (4).

Anal. Calcd for $C_{22}H_{26}S_6$: C, 54.73; H, 5.42; S, 39.84. Found: C, 54.91; H, 5.25; S, 39.93.

(*b*) *From the Z-thiosulfonate* **22a**. A solution of *p*-toluenethiol (0.291 g, 2.34 mmol) in CH_2Cl_2 (5 mL) was added (5 min) to a stirred solution of **22a** (0.500 g, 1.17 mmol) in CH_2Cl_2 (15 mL) at 0°C in the dark under Ar. After 10 min of additional stirring, solvent was removed, and the crude oil was chromatographed as in (a) to give 0.170 g (40%) of **14a** [Fraction I: R_f 0.52, 10% CH_2Cl_2 in hexane], and 0.023 g (8%) of **13** [Fraction II: R_f 0.31, 10% CH_2Cl_2 in hexane]. IR, MS, and NMR spectra of **14a** and **13** were identical to those of **14a** and **13** obtained from **16a** in (a).

E-1,4-Bis(p-tolyldithio)-2-butene (**15a, R = p-$CH_3C_6H_4$ −**).

(*a*) *From the E-Bunte salt* **16b**. Based on a procedure of Milligan and Swan for Na_2S,[3] a solution of *p*-toluenethiol (0.765 g, 6.16 mmol) in MeOH (50 mL) was added slowly (2 h) to the stirred solution of **16b**·0.1H_2O (1.00 g, 3.07 mmol) in pH 7 buffer solution (100 mL) containing 30% H_2CO solution (ca. 0.5 mL). After another 2 h of stirring, MeOH was removed, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). Flash chromatography of the crude product furnished as Fraction I, 0.750 g (67% yield) of white crystalline **15a**: mp 73–74°C; R_f 0.48 (10% CH_2Cl_2 in hexane); ^{1}H NMR ($CDCl_3$) δ 7.38–7.09 (dd, 8H), 5.57–5.54 (m, 2H), 3.27 (d, J = 6.0 Hz, 4H), 2.31 (s, 6H); IR (Nujol) 1640, 1600, 1490s, 1410, 1370, 1305, 1215, 1180, 1015, 975, 805s cm^{-1}; MS: m/z (rel. intensity, %) exact mass found 364.0449 (4), $C_{18}H_{20}O_4$ requires 364.0448, 280 (2), 278 (17), 247 (4), 214 (3), 211 (9), 210 (14), 209 (100), 189 (2), 187 (15), 177 (2), 157 (15), 154 (7), 124 (27.5), 123 (61), 122 (7), 121 (9), 118 (3), 111 (2), 109 (3.5), 108 (3).

Anal. Calcd for $C_{18}H_{20}S_4$: C, 59.30; H, 5.53; S, 35.17. Found: C, 59.41; H, 5.57; S, 35.19.

Along with **15a**, 0.047 g (6%) of **13** also was obtained as Fraction II; R_f 0.31 (10% CH_2Cl_2 in hexane); the IR and NMR spectra were identical with those of **13** in earlier experiments.

(*b*) *From the E-thiosulfonate* **22b**. In accordance with the procedure used for the preparation of **14a** from **22a**, treating **22b** (1.00 g, 2.34 mmol) with *p*-toluenethiol (0.581 g, 4.68 mmol) furnished 0.330 g (39%) of **15a** (Fraction I), along with 0.061 g (11%) of **13** (Fraction II) after chromatographic separation. The **15a** and **13** had R_f values, IR and NMR spectra identical with those shown by authentic samples.

Z-1,4-Bis(2'-3'-dihydroxypropyldithio)-2-butene [**14b, R = $-CH_2CH(OH)CH_2OH$**]. A solution of 3-mercapto-1,2-propanediol (0.189 g, 1.75 mmol) in CH_2Cl_2 (4 mL) was added (10 min) to the stirred solution of the thiosulfonate **22a** (0.300 g, 0.70 mmol) in CH_2Cl_2 (8 mL) at 0–5°C under Ar in the dark. After a stirring period of 20 min at 15°C, removal of the solvent and chromatography of the residue on a silica gel column (17-mm diameter × 15 cm) using 3–5% MeOH in CH_2Cl_2 yielded 0.023 g (10%) of **14b** as a semisolid: R_f 0.34 (10% MeOH in CH_2Cl_2); ^{1}H NMR (MeOH-d_4) δ 5.75–5.71 (m, 2H), 3.88–3.82 (m, 2H), 3.61–3.50 (m, 8H), 2.80–2.73 (4d, 8 lines, 4H); IR (neat) 3400s (br), 2940s, 1630, 1410s, 1335, 1290, 1210s, 1155, 1070s, 1030s, 915, 880, 780 cm^{-1}; MS (EI): exact mass found (m/z, relative intensity %) 214.0333 (30), $C_6H_{14}S_2O_4$ requires 214.0333; 117.9911 (18), $C_4H_6S_2$ requires 117.9911.

E-1,4-Bis(2',3'-dihydroxypropyldithio)-2-butene [**15b, R = $-CH_2CH(OH)CH_2OH$**]. By means of the procedure used for the *Z*-isomer **14b**, 0.300 g (0.70 mmol) of **22b** and 0.189 g (1.75 mmol) of 3-mercapto-1,2-propanediol furnished 0.023 g (10%) of white solid **15b**: mp 78–80°C; R_f 0.33 (10% MeOH in CH_2Cl_2); ^{1}H NMR (MeOH-d_4) δ 5.73–5.70 (m, 2H), 3.86–3.82 (m, 2H), 3.62–3.52 (m, 6H), 3.40–3.38 (m, 2H), 2.94–2.71 (m, 4H); IR (Nujol) 3350*s* (br), 1635, 1420, 1345, 1275, 1210, 1100s, 1070s, 1015s, 960, 930, 905, 875, 810, 760 cm^{-1}; MS: essentially identical to **14b**.

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